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McCUNE-ALBRIGHT SYNDROME

PENELOPE PHILBRICK FEUILLAN, M.D.

In its classic presentation, McCune-Albright syndrome (MAS) is the triad of polyostotic fibrous dysplasia, café-au-lait pigment, and precocious puberty which is due to gonadotropin-independent sex steroid secretion. The spectrum of additional endocrinopathies in MAS includes, most commonly, hyperthyroidism and goiter and, less frequently, acromegaly, hyperprolactinemia, Cushing's syndrome, and hypophosphatemic rickets. Some patients have also manifested hepatic, cardiac, and gastrointestinal dysfunction. Both sexes are affected, although the majority of reported cases have been young girls who present with breast development and menses (Table 1). MAS is presumed to be the result of a postzygotic mutational event occurring at the early embryonic stage of development. There is evidence that the abnormal cells in affected organ systems have activating mutations of the Gs_{α} subunit of the cAMP-linked signal transduction system. Additionally, high levels of proto-oncogene expression have been observed in bone lesions. These recent findings have focused the interest of both basic scientists and clinicians on this complex disorder.

Because of the broad spectrum in its clinical presentation, the diagnosis of MAS is not always obvious. The bone disease may be severe and progressive in early infancy, milder cases may manifest later in childhood as unequal limb length or facial asymmetry, and a few children have no signs or symptoms of fibrous dysplasia. In such cases the lesions become apparent only with technetium bone scan. Whereas the café-au-lait pigment typically appears as broad, irregular macules which often terminate abruptly at the ventral midline, it is occasionally confined to small areas in the nuchal region or the cleft of the buttocks. In 10 to 20 percent of patients, no abnormal pigmentation is found.

The precocious puberty in MAS characteristically presents as thelarche and/or vaginal bleeding in a girl under 2 to 3 years of age. Some girls have regular menses and rapid pubertal development, whereas others have intermittent bleeding which may not recur for months or years. In such patients, rates of growth and bone maturation can be normal, and puberty can occasionally occur at the normal age. The elevated serum estrogen levels in girls with MAS are due to ovarian cysts, which enlarge and resolve over periods of days to weeks. Baseline and gonadotropin-releasing hormone (GnRH)–stimulated LH and FSH are usually suppressed below the normal range. However, early in the course of the disorder, or when the ovarian activity is in remission, LH and FSH may be within the normal, prepubertal range. Some older patients, with bone ages over 11 to 12 years, have exhibited pubertal LH and FSH responses, presumably a result of maturation of the hypothalamic regulatory centers following sex steroid exposure.

Table 1 Abnormalities in McCune-Albright Syndrome

Disorder	*Frequency*
Endocrine	
Precocious puberty	+ + + +
Goiter/hyperthyroxinemia	+ + +
Acromegaly	+ +
Hypophosphatemic rickets	+
Cushing's syndrome	+
Hyperprolactinemia	+
Nonendocrine	
Café-au-lait pigment	+ + + +
Fibrous dysplasia of bone	+ + + +
Elevated hepatic transaminases	+ +
GI polyposis	+
Cardiomyopathy	+

+ + + +: >85%; + + +: 30–40%; + +: 3–5%; +: <3% in the NIH patient series.

Females with MAS appear to be at increased risk for developing breast cancers, possibly due in part to the prolonged estrogen stimulus or to the presence of mutation in the breast tissue itself. In this regard, MAS patients also appear to be at increased risk for thyroid and osseous malignancies. The physicians who care for these patients must be prepared to manage diverse forms of endocrine dysfunction and to coordinate with their surgical colleagues in treating the fractures and deformities that may be lasting sequelae of fibrous dysplasia of bone.

THERAPY FOR PRECOCIOUS PUBERTY

The decision to initiate therapy for precocious puberty in a girl with MAS is usually based on a history of recurrent menses, rapid pubertal development, and a significant degree of bone age advance (more than 2 SD above the chronologic age). Precocious puberty in most girls with MAS is gonadotropin independent and hence does not respond to treatment with the long-acting GnRH agonist analogues. My own clinical studies have focused on agents that block estrogen synthesis.

Testolactone

Testolactone (Teslac) is a competitive inhibitor of aromatase, the enzyme that converts testosterone and androstenedione to estradiol and estrone. This agent is a derivative of testosterone (a lactone ring is substituted for the D-ring of the steroid nucleus). Pilot studies showed decreases in serum levels of estradiol and estrone, a decrease in the frequency of menses, and a slowing in rates of growth and bone maturation in girls with MAS, and long-term clinical trials of testolactone have demonstrated continued benefit in several patients.

Pretreatment Evaluation

Before treatment is started, a GnRH stimulation test is performed to confirm gonadotropin-independent puberty. It is also helpful to measure baseline serum levels of estradiol and estrone, and of their biosynthetic precursors testosterone and androstenedione. Radiography of the hand and wrist should be done to determine bone age. Pelvic ultrasonography can document the presence and dimensions of ovarian cysts. A convenient method of quantifying the extent of ovarian cyst activity is to measure the mean ovarian volume (MOV). (V = length × width × thickness × 0.5; MOV = $V_{\text{right ovary}} + V_{\text{left ovary}} / 2$). Pretreatment laboratory studies should include thyroid hormone levels, thyroid-stimulating hormone, and tests of renal and hepatic function, because testolactone is metabolized in the liver and excreted in the urine (see Adverse Effects of Testolactone). The pretreatment evaluations are repeated at 6-month intervals during treatment.

Technetium bone scan is the most sensitive method for identifying sites of active bone disease. In patients with extensive bone involvement, short stature in adulthood is a consequence of both early epiphyseal fusion and also of the limb deformities, fractures, and scoliosis caused by fibrous dysplasia. Thus, in such a patient, an improvement in adult stature achieved by slowing the rate of bone age advance could be offset by the effects of her bone disease. Clinical trials have not shown whether treatment of the precocious puberty in MAS has an effect on the progression of bone lesions.

Treatment Protocol

Because girls may complain of abdominal pain and diarrhea early in the course of therapy, testolactone is begun at a low dose (10 mg per kilogram per day) and increased over a period of 3 to 4 weeks to the final oral dose of 40 mg per kilogram per day with divided doses given every 6 hours. If a patient has distress, the dose is reduced for 3 to 4 days. Most patients tolerate therapy well, although the frequent dosing schedule may be difficult to follow.

Patients who respond to treatment exhibit decreased levels of serum estrone and estradiol, decreased frequency of menses, and slowing in rates of growth and bone maturation. Because the natural course of precocious puberty in MAS is often intermittent, therapy should be continued for 6 to 12 months to estimate its effectiveness. In a patient who responds to testolactone, therapy is continued until the age of normal puberty or until bone age reveals epiphyseal fusion (bone age of 15 to 16 years).

Some girls who initially respond well to testolactone exhibit recurrent menses, ovarian cysts, and elevated estrogen levels after 2 to 3 years of therapy. The gonadotropin responses to GnRH in these girls may remain low or prepubertal, ruling out the onset of secondary central puberty. This apparent escape from control may represent tissue resistance to the effects of testolactone, an increase in metabolism and excretion, or, in some cases, decreased compliance.

Adverse Effects of Testolactone

In girls with MAS the only adverse effect attributable to testolactone, other than transient cramping and diarrhea, has been an increase in serum levels of hepatic transaminases (SGOT, SGPT, and GGTP) in one patient with pre-existing elevation of these enzymes and biopsy-proven liver disease. The transaminase levels returned to their pretreatment levels on discontinuation of testolactone, and there was no clinical evidence of deteriorating liver function; however, it is important to confirm normal hepatic function prior to initiation of testolactone treatment.

No MAS patient has developed evidence of androgen excess, and the serum levels of androstenedione and testosterone have remained low or in the pubertal range. The presence of testolactone metabolites may, however, lead to elevations in urinary 17-ketosteroid and 17-hydroxysteroid measurements.

Newer Drugs

Clinical trials of a nonsteroidal competitive inhibitor of aromatase, fadrozole hydrochloride, are under way in girls with gonadotropin-independent precocious puberty. Because of the lower daily dose and the twice daily dosing schedule, it is hoped that use of this agent will bring about improvement in compliance and more effective suppression of serum estrogen levels.

Nonsteroidal estrogen antagonists such as Tamoxifen have not been studied extensively in girls with precocious puberty. The safety of these agents for long-term use in pediatric patients has not been established.

SECONDARY CENTRAL PUBERTY

A few girls with MAS and bone ages close to the pubertal range (older than 11 years) exhibit a pubertal pattern of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responses after GnRH before or during treatment, indicating the onset of gonadotropin-dependent puberty. In these patients, therapy with one of the long-acting GnRH agonists may be added to the testolactone regimen in order to suppress pituitary gonadotropin secretion. The depot preparation of leuprolide acetate offers the most convenient approach to treatment. The usual dose is 7.5 mg (300 to 500 μg per kilogram) every 28 days, but many patients require larger doses. Abscess formation is an occasional complication. There is also extensive clinical experience with the potent GnRH agonists histrelin (Supprelin; 10 μg per kilogram per day SC), which is now commercially available for children with central precocious puberty, and with deslorelin (Somagard, 4 μg per

kilogram per day), which will be available within a short time.

A GnRH stimulation test is performed at 3- to 6-month intervals after initiating treatment with the LHRH analogues in order to confirm that gonadotropin levels are suppressed.

As yet, there are no studies demonstrating the long-term effectiveness of combined therapy using aromatase inhibitors together with GnRH analogues in girls with precocious puberty due to MAS.

ALTERNATIVE TREATMENTS

Medroxyprogesterone Acetate

Medroxyprogesterone acetate is a progestin that has been used to control menstrual bleeding in girls with precocious puberty and that may be effective for this purpose in girls with MAS who fail to respond to other treatments. The preferred form is the depot preparation (Depo-Provera), which is administered intramuscularly at a dose of 50 to 200 mg (4 to 15 mg per kilogram) once a month. There are no long-term studies of the efficacy of medroxyprogesterone acetate in the treatment of groups of girls with MAS, however, and no evidence that it can slow the rate of bone maturation. At high doses, it can suppress adrenocortical function, and it has also been linked to the occurrence of tumors in experimental animals.

Surgery

Ovariectomy or ovarian cystectomy should be considered a last resort for treating precocious puberty due to MAS, because cysts almost always recur in the remaining ovarian tissue. There is also a potential loss of fertility (some adult women with MAS are able to conceive, and most bear normal children) as well as the risks associated with anesthesia and scarring and adhesions.

MALES WITH MAS

Precocious puberty due to autonomous testicular hyperfunction, together with the skin, bone, and endocrine manifestations of MAS, is occasionally seen in males. Since pubertal development and rates of linear growth and bone maturation in boys are mediated by both androgens and estrogens, therapy for boys with MAS is directed at both classes of sex steroid. This form of treatment has been used in boys with the gonadotropin-independent familial form of male precocious puberty (FMPP), also referred to as testotoxicosis. (See the chapter Familial Male Precocious Puberty.)

Spironolactone, a blocker of androgen action, is given at a daily dose of 5.7 mg per kilogram. Although no important adverse effects have been observed at this dose, patients are monitored carefully for evidence of mineralocorticoid deficiency and electrolyte imbalance and are instructed to discontinue drug during periods of acute illness.

The aromatase inhibitor testolactone (see Testolactone) is given in conjunction with spironolactone to block estrogen biosynthesis. This combined therapy has been effective in controlling the precocious puberty in FMPP. In addition, gynecomastia, a common secondary effect of antiandrogen treatment, does not occur in patients receiving both spironolactone and testolactone.

As in girls with MAS, pretreatment evaluations include a GnRH stimulation test, levels of testosterone and estradiol, and tests of hepatic and renal function. Patients are monitored at least every 6 months, including serum electrolyte levels in those taking spironolactone. In boys whose gonadotropin responses after GnRH indicate the advent of secondary, central puberty, therapy with one of the GnRH agonists is added to the regimen.

Alternative antiandrogenic agents include the antifungal agent ketoconazole (Nizoral), which has been used at a dose of 600 mg per day in the treatment of boys with FMPP. Ketoconazole was well tolerated in this group of patients, although it is known to have antiglucocorticoid actions and has been associated with hepatic damage in small numbers of subjects.

COST OF MEDICATIONS

Most of the available agents used to treat precocious puberty are expensive. The approximate yearly cost* of treating a 30 kg child at the usual doses is as follows: testolactone, $10,800.00; leuprolide depot, $5,730.00; histrelin, $4,320.00; medroxyprogesterone acetate, $355.00; ketoconazole, $3,000.00; spironolactone, $75.00 to $235.00.

THYROID ABNORMALITIES

Thyroid abnormalities are found in 30 to 40 percent of patients with MAS; the incidence is reported to be higher in males. Characteristically, the serum TSH levels are low or undetectable, the thyroid hormone levels normal or elevated, and structural abnormalities such as hypoechoic or hyperechoic regions (indicative of cysts or nodules) are seen on ultrasonography. In children and young adults, the thyroid disorder often takes an indolent course; goiter may remain inapparent or develop gradually and patients may remain clinically euthyroid for years. No long-term studies have yet revealed what percentage of these patients will eventually require medical intervention.

In the event of symptomatic hyperthyroidism, administration of a thionamide such as propylthiouracil (PTU) or methimazole can reduce serum thyroid hor-

*Based on wholesale prices from 1995 Drug Topics Red Book, Montvale, NJ.

mone levels and normalize TSH. The doses used in MAS patients are comparable to those in patients with Graves' disease (3 to 6 mg per kilogram per day in children, 300 to 600 mg per day in adults, divided every 6 to 8 hours). The yearly cost of treating a 30 kg child is $25.00 to $75.00.

The risk of adverse reactions to PTU, such as agranulocytosis and granulocytopenia, appears to be no greater in MAS than in other patients.

Thyroidectomy or hemithyroidectomy has historically been the definitive therapy for hyperthyroidism and goiter in MAS patients. Radioiodine has also been used effectively for thyroid ablation.

GROWTH HORMONE AND ACROMEGALY

Growth hormone (GH) hypersecretion is an uncommon finding in MAS and is usually not identified until patients have reached early or mid-adulthood. In children a rapid rate of linear growth and elevated serum levels of insulin-like growth factor-1 (IGF-1) may be attributed to the elevated levels of sex steroids. In many patients, the facial features of acromegaly may be obscured by the skull and facial deformities caused by fibrous dysplasia. The diagnostic criteria are similar to those of non-MAS patients with acromegaly. In affected subjects, serum IGF-1 levels are elevated, GH levels do not fall or may rise paradoxically following an oral glucose load, and there may be paradoxical stimulation of GH after thyrotropin-releasing hormone.

Octreotide is a long-acting somatostatin analogue that has been used successfully to suppress GH secretion in acromegaly, including small numbers of patients with MAS. The daily dose of octreotide is usually 300 μg SC, divided in three doses. Side effects of treatment have included abdominal pain and nausea in the early weeks of treatment, and a 65 percent and 20 percent incidence of bile sludge formation and gallstones, respectively. The yearly cost of treatment is approximately $8,500.00.

Bromocriptine, the dopamine agonist that is used to treat hyperprolactinemia and prolactinoma, has not been used with success for suppressing GH in MAS. Pituitary adenomectomy is often impractical due to the presence of fibrous dysplasia in the sellar region, and clinicians hesitate to use radiation therapy because of reports of osteogenic sarcoma and other bone neoplasms in MAS patients.

HYPOPHOSPHATEMIA AND RICKETS

Those who care for patients with MAS should keep in mind that the onset of rickets may be obscured by the radiologic and hematologic stigmata of the bone disease. The serum calcium levels in MAS patients are typically normal, and the serum phosphorus may be normal or low normal. The serum alkaline phosphatase and urinary hydroxyproline levels range from normal to very elevated because of polyostotic fibrous dysplasia; these laboratory indices do not always correlate with the extent of skeletal involvement, however.

The diagnosis of rickets in MAS is usually based on the classic radiologic stigmata of epiphyseal widening, cupping, and fraying. In some cases, serum parathyroid hormone (PTH) may also be elevated. Treatment is comparable to the treatment of other forms of hypophosphatemic rickets; vitamin D is usually administered as calcitriol ($1,25\text{-}(OH)_2D_3$) at an initial dose of 0.250 μg given twice daily, together with a phosphorus preparation such as K-Phos, 250 mg, 4 to 6 times daily. Patients are carefully monitored for hypercalcemia, renal stone formation, and secondary hyperparathyroidism. The yearly cost of calcitriol is approximately $800.00.

HYPERADRENOCORTICISM AND CUSHING'S SYNDROME

Autonomous adrenocortical hyperfunction causing Cushing's syndrome is a rare complication of MAS; most of the reported cases have occurred in infants under 3 months of age. Bilateral adrenalectomy was performed in these patients, followed by mineralocorticoid and glucocorticoid replacement therapy. As yet there are no reports of successful medical management of Cushing's syndrome in MAS patients, although antiglucocorticoid agents such as ketoconazole and the antiprogestin RU-38486 have been used for this purpose in other pediatric patients. My own experience with a girl with MAS who had hypercortisolemia and cushingoid appearance in infancy, followed by normal adrenocortical function later in childhood, suggests that some patients could be managed conservatively.

POLYOSTOTIC FIBROUS DYSPLASIA

The bone disease in MAS can have devastating consequences, causing facial and limb deformity, fractures, scoliosis, and pain. In my own group of pediatric patients, rapidly expanding cranial lesions have been associated with blindness caused by optic nerve compression in one girl and galactorrhea with normal prolactin levels in another.

Although no form of medical treatment has yet been proven to alter the course of the bone disease, recent studies indicate that bisphosphonate therapy can alleviate pain and improve the radiologic picture in fibrous dysplasia of bone, and trials are now under way to test its effectiveness in patients with MAS.

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TURNER'S SYNDROME

PAUL SAENGER, M.D.

Turner's syndrome is one of the most common chromosomal abnormalities, with an estimated frequency of 3 percent among early female fetuses. Because of a yet-unexplained propensity for spontaneous miscarriage, the female live birth frequency of 45X fetuses is only 1 in 1,500 to 1 in 2,500. This results in an estimated 50,000 to 75,000 children and women with Turner's syndrome in the United States alone. Early lethality of 45X may result from placental dysfunction. In the absence of the Y chromosome the indifferent gonad develops into the embryonic ovary. Germ cells exist in 45X fetuses, but 45X oocytes undergo attrition more rapidly than 46XX oocytes.

Turner's syndrome is best defined by a cytogenetic criterion: complete or partial absence of the second sex chromosome with or without cell line mosaicism. At birth the well-described characteristic physical features are frequently present but may not be (Table 1).

45X is still the single most common karyotypic finding in about 50 percent of individuals with Turner's syndrome. The most common forms of mosaicism are 45X/46XX and 45X/46X_i (X_q). Mosaicism may modify the phenotype toward normal. Therefore, all individuals with suspected Turner's syndrome should be karyotyped. Sufficient cells should be counted to exclude low-percentage mosaicism. It is recognized that this cannot be totally excluded. Usually a peripheral blood karyotype is adequate. Probing for cryptic Y material should be performed in any Turner's syndrome patient with any evidence of virilization or when a marker chromosome (a chromosomal fragment of uncertain origin) is found. This can be achieved by DNA hybridization, polymerase chain reaction (PCR) techniques, or fluorescent in situ hybridization (FISH), using a Y centromeric or short-arm probe. Inexpensive analysis of Y chromosomal material may become available in the future, allowing for routine screening of all the individuals with Turner's syndrome in whom there is a possibility of Y-bearing cells.

In patients with occult Y chromosomal material and Y gonadal dysgenesis or mixed gonadal dysgenesis (45X/46XY), the incidence of dysgerminoma is high, and gonadal tissue should be removed. The risk of gonadoblastoma in the second and third decade of life has been estimated to be as high as 30 percent.

PEDIATRIC MANAGEMENT

Most prenatally detected cases of Turner's syndrome are discovered incidentally during chorionic villous biopsy or amniocentesis performed for unrelated reasons, most commonly because of advanced maternal age or because of prior congenital anomalies in the offspring. Advanced maternal age in itself is not associated with an increased incidence of Turner's syndrome. Current data indicate that many fetuses diagnosed prenatally with Turner's syndrome are electively terminated.

Prenatal counseling centers on a detailed discussion of the variability of somatic anomalies and the very high likelihood of short stature and ovarian failure. Newer therapeutic approaches outlined below should emphasize that individuals can be healthy, happy, and productive members of society.

As soon as Turner's syndrome is diagnosed the cardiac anatomy must be evaluated. Both ultrasound and magnetic resonance imaging (MRI) have been used. MRI has been more useful for the diagnosis of aortic abnormalities. Echocardiography must be carried out by an experienced echocardiographer because of the congenital abnormalities of the chest (shield chest), which may make imaging more difficult. If coarctation of the aorta is detected, it will be surgically corrected. Patients with a bicuspid aortic valve are at a greater risk for progressive dilation of the aortic root diameter in later life and should, therefore, be monitored more carefully. Prophylactic antibiotics for prevention of subacute bacterial endocarditis in these patients with cardiac abnormalities undergoing dental procedures, such as cleaning, are strongly recommended.

All Turner's syndrome patients should have a renal ultrasound performed at the time of diagnosis. If any structural abnormalities are detected, proper evaluation and therapy should be instituted. In individuals with structural abnormalities, urine cultures should be performed at regular intervals to treat silent infections promptly.

Hypertension is common in Turner's syndrome even